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Research Article

Combining population projections with quasi-likelihood models: A new way to predict cancer incidence and cancer mortality in Austria up to 2030

Johannes Klotz **Alexander Hanika**

Monika Hackl **Daniela Haluza**

Markus Schwab

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Johannes Klotz[1‡]
Monika Hackl[1‡]
Markus Schwab[2]
Alexander Hanika[1]
Daniela Haluza[2*]

Abstract

BACKGROUND
The current demographic changes with a shift toward older ages contribute to more cancer cases in the next decades in Western countries. Thus, forecasting the demand for expected healthcare services and expenditures is relevant for planning purposes and resource allocation.

OBJECTIVE
In this study, we provide a new method to estimate future numbers of cancer cases (newly diagnosed cancers and cancer deaths) using Austrian data.

METHODS
We used 1983–2009 data to estimate cancer burden trends using quasi-Poisson regression models, which we then applied to official population projections up to 2030. Specific regression models were estimated for cancer incidence and mortality, disaggregated by sex and 16 tumor sites.

RESULTS
The absolute number of cancer cases increased continuously during the last decades in Austria. The trend will also continue in the near future, as the number of newly diagnosed cancers and cancer deaths will increase by +14% and +16% between 2009 and 2030. Age-standardized individual risk of being newly diagnosed with or die from

[1] Statistics Austria, Vienna, Austria.
[2] Department of Environmental Health, Center for Public Health, Medical University of Vienna, Austria.
[*] Correspondence to daniela.haluza@meduniwien.ac.at.
[‡] Authors contributed equally.

cancer will be substantially lower in 2030 compared to 2009 (–14% and –16%, respectively).

CONTRIBUTION

Our novel method combining population projections with quasi-likelihood models found a falling individual risk for cancer burden in the Austrian population. However, the absolute number of new cancer cases and deaths will increase due to the aging of the population. These estimates should be considered when planning future healthcare demands.

1. Introduction

Health planners rely on cancer predictions to optimize allocation of limited resources for primary prevention, screening, treatment, rehabilitation, and palliative care. The most common types of cancer are lifestyle-related, and thus largely preventable (Anand et al. 2008). From a public health perspective, predictions show the effect of health promotion and cancer prevention programs aimed at reducing the burden of cancer in the targeted population (Moller et al. 2007). Changes in population size and structure and changes in individual cancer risk are relevant parameters for anticipating trends in future cancer cases (Bray and Moller 2006). Population-wise changes also depend on immigration and emigration. Given the current demographic trends toward increasing life expectancy, low birth rate, and the baby boomer generation advancing in years, the utmost important time-related variable influencing cancer trends is age. An aging organism accumulates exposure to carcinogens (external factors) and also cancer-inducing spontaneous cell mutations and genetic instability (internal factors) (Finkel, Serrano, and Blasco 2007).

Future changes in disease rates are generally estimated on the basis of those observed in the past. In that respect, a crucial question is to what extent past developments were shaped by the evolution of risk factors (e.g., smoking), population characteristics (e.g., age structure, migrant population), measurement problems (e.g., under-registration of events), and other relevant issues (e.g., outcome-related latency periods), for these influences may evolve differently in the future. A model that fits the data does not necessarily have to provide successful predictions, but a prediction from a model that does not fit past observations is rarely adequately predictive (Valls et al. 2015).

Several statistical methods and estimation techniques, such as Poisson regression or logistic regression, are used for projecting the future cancer burden of a particular nation. In contrast to assuming the perpetuation of past rates of change projections,

more complex models incorporate the past components of change due to age, period, and birth cohort effects (O'Brien 2000; Olsen, Parkin, and Sasieni 2008). In the United Kingdom, as an example, previous studies have employed such models to generate cancer mortality projections up to 2025 (Olsen, Parkin, and Sasieni 2008; Mistry et al. 2011) and cancer incidence projections up to 2020 (Moller et al. 2007).

In Austria, the proportion of the population aged 65+ will grow from 18% in 2012 to 24% by 2030, mainly as a result of the aging of the baby-boom generation born in the late 1950s and early 1960s. This means that Austria will face significant population aging in the near future. Consistent and accurate data as found in Austrian databases are vital for estimating trends in cancer incidence based on cancer registration data (Doll and Peto 1981). So far, estimates of the corresponding future burden of cancer in terms of numbers of cases are lacking. Thus, we aimed at predicting future cancer cases in Austria for 2010–2030 using 1983–2009 data from the Austrian National Cancer Registry, the Austrian Causes of Death Statistics, and the Population Projections by Statistics Austria. For that purpose, we introduced a new statistical approach of a secondary population projection to predict cancer incidence and cancer mortality of all tumor sites accounting for the available Austrian data.

2. Materials and methods

2.1 Terminology

We use the term 'population projections' for outcomes on future population size and structure obtained by combining a baseline population with assumptions on future fertility, mortality, and migration (deterministic what-if statements) (Preston, Heuveline, and Guillot 2000). We further use the term 'forecasts' for future outcomes obtained by a statistical model that allows also for conducting significance tests and generating confidence intervals (probabilistic statements). A 'primary' population projection is restricted to demographic outcomes (age, sex, and region) as direct results of demographic processes. A 'secondary' population projection is obtained by applying additional structural variables (such as having cancer) to primary projections. Thus, we aimed at predicting future cancer incidence and cancer death counts by a secondary population projection, multiplying projected population figures with forecasted cancer incidence and mortality rates.

2.2 Data

2.2.1 Primary population projection

Statistics Austria, the Austrian national statistical institute, regularly publishes long-run cohort-component population projections by sex, age, and nine NUTS-2 regions, i.e., Burgenland, Carinthia, Lower Austria, Upper Austria, Salzburg, Styria, Tyrol, Vorarlberg, and Vienna (Statistik Austria 2014). Several variants are published, combining high, medium, and low-level assumptions on future fertility, mortality, and migration. The main variant of population projections combines medium assumptions on each demographic process, for it is understood to be the most likely future path of the Austrian population. So this variant assumes a slight increase in period fertility, a continuous increase in life expectancy, and enduring positive net migration over the next decades. Details on assumptions and methods are described elsewhere (Hanika 2013). Herein, we used the main variant of the 2013 generation of population projection to 2030, as uncertainty of the forecasted cancer incidence and mortality rates with which the primary population projection is combined would increase for later years – not so much in terms of statistical prediction error, but regarding the stability of structural relationships in the regression specifications. The most important outcome of the primary population projection is a substantial increase in the elderly population (65+ years) from just over 1.5 million in 2013 to almost 2.2 million in 2030. Besides increasing life expectancy, the main driver of this demographic change is the aging of the baby boomer cohorts.

2.2.2 Austrian National Cancer Registry

The Austrian National Cancer Registry is a population-based cancer registry that provides data on cancer incidence, survival, and prevalence. Data has been published since the year of diagnosis 1983 because, since then, individual records can be linked to the Austrian Cause of Death Statistics, which is essential for completeness of registration. Reporting newly diagnosed cancer cases to the Austrian National Cancer Registry is mandatory by law for all Austrian hospitals.

Cancer incidence count is the annual total of newly diagnosed tumor diseases in Austria. Austrian hospitals are obliged to report any newly diagnosed tumor disease to the Austrian Cancer Registry by a standardized form. Tumors of patients not living in Austria and those only diagnosed by physicians in private practices or by foreign hospitals are excluded from the incidence count. The same person may be registered several times with different tumor diseases. Tumors may be diagnosed at different

stages. Cancer incidence data is enriched by death certificate only (DCO) cases, i.e., when the death certificate of a deceased person who was not registered in the cancer registry indicates a tumor disease. The tumor information in the database of the Austrian National Cancer Registry is coded according to International Classification of Diseases O-3 (ICD-O-3). When moving to a new classification, e.g., from ICD-O-2 to ICD-O-3, the whole database is recoded using the free software CanReg5 for cancer registry data input, storage, and analysis (CanReg5 2016). ICD-10 codes are added to the data when extracted from the database by using this multi-user, multi-platform, open-source tool produced by the International Agency for Research on Cancer in collaboration with the International Association of Cancer Registries (IARC/IACR).

Currently, there are about 38,000 newly diagnosed cancer cases per year in Austria, thereof 20,000 among men and 18,000 among women. The most frequently diagnosed cancers are prostate cancer, lung cancer, and colon cancer among males, and breast cancer, lung cancer, and colon cancer among females. Around 9% of the total incidence count is DCO cases, with some variation between NUTS-2 regions.

2.2.3 Austrian Cause of Death Statistics

Since 1945, the collection of death records (including cause of death) in Austria is based on administrative records of 1,400 civil registry offices, which in turn are based on reports from hospitals and medical examiners who deliver medical and demographic characteristics and information on cause of death. Death registration is mandatory by law and virtually complete, although deaths of Austrian residents dying abroad were insufficiently covered before 2009.

The Austrian death certificate contains – in addition to the information on the immediate cause and the underlying cause of death – information on the course of the diseases. In Austria, mono-causal causes of death are recorded, which means that only the underlying cause is coded by a trained team according to ICD-10. The death certificate can be issued only by officially appointed physicians, pathologists, or coroners. Therefore, the quality of the cause of death statistics depends on the quality of the data provided by medical doctors. In most cases clinical diagnoses are used to describe the cause of death. An autopsy is performed in about one-tenth of all deaths.

Around 20,000 cancer deaths are recorded annually in Austria, thereof 11,000 among men and 9,000 among women. The most important tumor sites are lung cancer, prostate cancer, pancreas cancer, and colon cancer among males, and breast cancer, lung cancer, pancreas cancer, and colon cancer among females.

2.2.4 Tumor sites

Cancer is partitioned into 16 tumor sites for this projection. Out of the 16 tumor sites, 13 are applicable to males and 15 to females. Details on the disaggregation, including ICD-10 codes, are given in Table 1. Traditionally, head and neck cancers were classified as ICD-10 C00–C10 and C31–C32 in Austria, and this was still the case when we queried our data. Just recently, the definition of head and neck cancers was changed to C00–C14 to enhance international comparability of the data, which however did not influence the predictions presented herein. We forecast cancer incidence and cancer mortality rates for each sex and tumor site, so in total we estimate (13 + 15) × 2 = 56 models.

Table 1: Tumor sites, ICD-10-codes and starting years of base periods

		Starting year of base period			
		Incidence		Mortality	
Tumor site	ICD-10 code	Males	Females	Males	Females
Head and neck	C00–C10, C31–C32	1994	1994	1986	1983
Stomach	C16	1983	1983	1983	1983
Colon, rectum, and anus	C18–C21	1996	1998	1996	1998
Pancreas	C25	1983	1983	1994	1994
Trachea, bronchus, and lung	C33–C34	1983	1983	1983	1983
Melanoma of skin	C43	1983	1983	1983	1983
Breast	C50	1983	1997	1983	1997
Cervix uteri	C53	–	1983	–	1983
Corpus and uterus, not other specified	C54–C55	–	1994	–	1983
Ovary	C56	–	1995	–	1995
Prostate	C61	2000	–	2000	–
Kidney	C64	1991	1993	1991	1993
Bladder	C67	1997	1998	1983	1999
Brain and nervous system	C70–C72	1983	1998	1983	1983
Lymphoid, hematopoietic, and related tissue	C81–C96	1995	1997	1983	1983
Other and unspecified	Other C, excl. C44	1983	1983	1993	1993

Source: Own calculations.
Note: The end year of each base period is 2009.

2.3 Forecasting cancer incidence and cancer death rates

The Austrian National Cancer Registry has published data on cancer incidence since the year of diagnosis 1983. At the time of data query (17 October 2013), the latest year considered to be of sufficient data quality (completeness of registration) was the year of diagnosis 2009. Thus, we used the calendar years 1983–2009 as the base period for

model estimation and then applied estimated parameters to the calendar years 2010–2030 for predictions.

2.3.1 Quasi-Poisson regression with offset parameter

All 56 models conditional on sex, tumor site, and incidence/mortality are quasi-Poisson regression models with exponential mean function, or equivalently, log-link function (McCullagh and Nelder 1989; Cameron and Trivedi 1998).

In a general sense, denote by P the size of the risk population (i.e., the person-years lived during a calendar year), by Y the cancer count of interest (either newly diagnosed cancer cases or cancer deaths), by t the calendar year, and by x a column vector of other explanatory variables such as age group or region (details are given below). Then our model (1) assumes that

$$E(Y|P,t,x) \coloneqq \mu = P \times \exp(t\theta + x'\beta), \tag{1}$$

with θ and β the parameters to be estimated.

The exponential mean function specification means that regression parameters are semi-elasticities, implying that an increase of time by one calendar year means a constant percentage change in the expected value of Y, holding other factors constant. This assumption is natural for count data, which also guarantees non-negative predictions. The mean function specification was checked by graphical inspection of residuals.

In model (1) population, size P is an offset variable. The ratio Y/P denotes the rate of cancer incidence or mortality. For the years 1983–2012, population sizes were known from Austrian population statistics data. For the years 2013–2030, the projected values obtained by the primary population projection as described above were applied. As mentioned before, cancer incidence refers not only to first-time tumor diseases, but the same person may be diagnosed several times with different tumor diseases. So, in any given year, the entire Austrian (observed or projected) population is at risk of being newly diagnosed or dying from cancer.

Model (1) could be estimated by an ordinary Poisson regression model. However, Poisson regression is based on the rather strong assumption of identic conditional mean and variance (equidispersion). This implies that all regressors that influence the conditional mean are known and included in the model without any measurement error. In practice, this assumption is almost always violated, at least for some tumor sites. It is therefore necessary to allow for overdispersion in count data to obtain correct standard errors and confidence intervals (Winkelmann 2010). There are many possible options to

account for overdispersion. A straightforward technique is quasi-Poisson regression, which is an instance of Generalized Linear Models (McCullagh and Nelder 1989; Cameron and Trivedi 1998). Quasi-Poisson regression assumes that

$$Var(Y|P,t,x) = \mu \times \varphi, \tag{2}$$

with φ the dispersion parameter. A value greater than 1 means overdispersion.

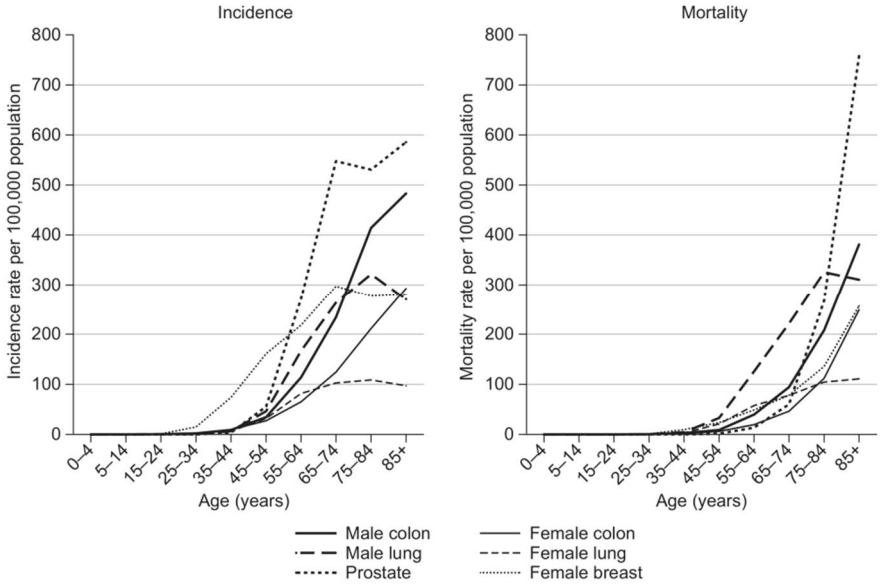
So the conditional variance of the cancer count of interest is not identical but proportional to its conditional expectation. In quasi-likelihood terms, the nominal Poisson variance μ accounts for pure chance fluctuations, whereas the dispersion parameter φ accounts for unobserved heterogeneity in the conditional mean (Winkelmann 2010).

2.3.2 Regressors used in all models

All 56 regression models included a time trend operationalized by the calendar year. The Austrian National Cancer Registry started to publish data for the year of diagnosis 1983, and 2009 was considered the latest year of sufficient data quality (completeness of registration). We estimated the trend parameter from 1983–2009 and then applied the estimated parameter to the 2010–2030 period. However, graphical (human eye) inspection of age-standardized rates revealed structural breaks within the 1983–2009 period for some tumor sites. For example, female breast cancer incidence increased sharply until the mid-1990s but has remained rather constant since. So the starting year of the base period was in some instances chosen later than 1983, as shown in Table 1. We specified 2000 as the latest possible starting year of the base period so that any base period covers at least ten calendar years, and all base periods end in 2009.

Most (but not all) cancers are strongly age-dependent, with incidence and mortality risk usually increasing from lower to higher ages. Age profiles for the most frequent tumor sites are given in Figure 1. To account for this variation, we partitioned our data into ten age groups, namely 0–4, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84 years, respectively, and 85 years and older. We estimated separate regression parameters for each age group except, for some tumor sites, the youngest age groups were pooled due to small numbers. Details can be found in Table A-1.

Figure 1: Age profiles of incidence and mortality of selected cancers



Cancer incidence and mortality rates vary between the nine NUTS-2 regions. Also, the Austrian health system is to some degree decentralized. To account for that we included regional dummies in each model, as suggested by Dyba and Hakulinen (2008).

Furthermore, past trends in cancer incidence and mortality rates showed some regional variation. For instance, skin cancer incidence has increased less sharply (albeit from a higher starting level) in Vienna than in the other regions. It was thus questionable whether the same time-trend parameter should be applied to all regions. We decided on a mixed approach. First, we estimated separate trend parameters for each region. Then, we tested for (Bonferroni-adjusted) significant differences between these regional trends. If the regional trends were not statistically different, the same trend parameter was applied to all nine regions. Otherwise, we grouped regions according to parameter estimates and geographic location and then estimated a separate trend for each group of regions. Details on grouping can be found in Table A-2.

Table 2: Special regressors used in some models

Tumor site	ICD-10 code	Explanatory variable	Interpretation
Incidence			
All cancers	C00–C97, excl. C44	Dummy for region Styria since 2006	Increase of completeness of case ascertainment due the use of an additional pathology database
		Dummy for region Tyrol since 1988	Regional cancer register established
		Dummy for region Carinthia since 1993	Regional cancer register established
		Dummy for region Carinthia in 1995–1998	Regional cancer register established, but lower completeness during initial years
Colon, rectum, and anus	C18–C21	Dummy for region Burgenland since 2006	Regional screening program
Melanoma of skin	C43	Trend for region Tyrol 2000–2008; separate dummy since 2009	Different registration practices, involving primary care
Prostate	C61	Dummy, trend, and squared trend for region Salzburg in 1998–2009	Regional screening program
		Dummy, trend, and squared trend for region Vorarlberg 2001–2009	Regional screening program
		Dummy, trend, and squared trend for region Tyrol in 1991–2008; separate dummy since 2009	Regional screening program
Mortality			
All cancers	C00–C97, excl. C44	Dummy since 2002	Change ICD-9 to ICD-10
		Dummy since 2004	New death certificate

2.3.3 Special regressors used in some models

The data available for the base period contained the reported number of cancer cases (incidence and mortality) for a specific site. Changes in reporting behavior during the base period thus influence observed trends. To give an example, introducing regional cancer registries clearly increased completeness of ascertained cases for reported regional cancer incidence rates (Hackl and Waldhoer 2013). A challenge in forecasting incidence and mortality rates is to disentangle such data artifacts from real trends, for only the latter should be used in forecasts. Regarding cancer incidence, we identified several influences on reporting behavior in the 1983–2009 period. In particular, two regions introduced regional cancer registries with substantial impact on completeness, and four regions introduced regional screening programs for specific tumor sites.

Predictors that were included in only some of the 56 models are given in Table 2. We modeled the presence of a regional cancer registry by a dummy variable, assuming that its effect on the measured cancer incidence count is essentially a one-shot shift in completeness (except in one instance, where we also accounted for some initial problems with the regional registry).

In the case of screening programs, the situation is somewhat different. Typically, screening programs first take some time to ramp up and then cause a temporary

incidence bulk when tumors are diagnosed earlier than before. Ultimately, a screening program should merely increase completeness. We therefore accounted for both short-run and long-run effects of screening programs by including a quadratic trend in the first years of the program (except in one instance, where the screening program only started in 2006) and a dummy variable for the entire period of the program.

Regarding cancer mortality, the change in ICD version from revision 9 to revision 10 and the use of a new death certificate could matter for some tumor sites in particular. So we included dummy variables for the years after 2001 (change in ICD) and for the years after 2003 (new death certificate).

2.3.4 Software implementation and prediction

Population data (observed for 1983–2012, projected for 2013–2030), cancer incidence counts from the Austrian National Cancer Registry (date of query: 17 October 2013), and cancer death counts from the Austrian Cause of Death Statistics were processed in SAS, Version 9.3 (SAS Institute Inc., Cary, North Carolina, USA). The statistical models (1) were estimated by the GENMOD procedure. Dispersion parameters in equations (2) were estimated by dividing the generalized chi-square statistics by its degrees of freedom (Cameron and Trivedi 1998).

Estimated regression parameters $\hat{\theta}$ and $\hat{\beta}$ were applied to projected population figures to forecast future cancer incidence and cancer death counts:

$$\hat{Y} = P \times \exp\left(t\hat{\theta} + x'\beta\right). \tag{3}$$

Note that predicted counts are generally not integer-valued.

To obtain overall (all-site) predictions of future cancer incidence and cancer death counts, we summed up the site-specific predictions over all sites.

Absolute values of future cancer incidence and death counts are important for healthcare planning and resource allocations. Besides such aggregate outcomes, from a Public Health perspective it is also important to predict the evolution of individual risks. For that purpose we computed age-standardized rates of cancer incidence and mortality by direct age standardization based on the WHO World 2000–2025 Standard Population (Ahmad et al. 2001).

We used Xact pro software, Version 8.0 (SciLab, Hamburg, Germany) and Microsoft Excel 2010 (Microsoft Corporation Redmond, Washington, USA) for graphical data presentation.

2.4 Sensitivity analysis: Constant rates scenario

Given the projected substantial increase in the elderly population in the coming decades, aggregate cancer counts in the population might increase despite falling individual risk if the decline in individual risk is numerically over-compensated by population aging. An interesting question in that respect is the effect of population aging alone, i.e., how future cancer incidence and mortality counts would evolve if individual risk remained constant in the future. For that purpose, we made an alternative prediction based on a constant rates scenario that keeps age-specific cancer incidence, cancer mortality, and all-cause mortality rates constant over the entire prediction period. We used a three-year average 2008–2010 to minimize random fluctuations. The deviation between our prediction (3) and the values obtained by the alternative constant rates scenario then indicate to what extent changes in risk behavior, as well as medical and social progress (which are implicitly included in the time-trend parameters), alter the future evolution of cancer counts that would result purely from age structure changes.

3. Results

3.1 Estimated regression parameters

Across all 56 quasi-Poisson models combined, we estimated more than 1,000 regression parameters. Presenting all of them is beyond the scope of this paper and, more importantly, most of them are not of particular interest. We thus present one exemplary model (incidence of head and neck cancer for males) and then give in detail the estimated trend parameters for all models. All estimated regression parameters and their estimated standard errors are available on request from the authors. Dispersion parameters are given in Table A-3.

Table 3: Estimated regression model for male head and neck cancer incidence

Predictor	Estimated maximum quasi-likelihood parameter	Estimated asymptotic standard error	P-value	Estimated incidence rate ratio
Logged person-years lived	1			
Intercept	–7.26	0.08	***	
Age group				
0–34 years	–4.88	0.12	***	0.01
35–44 years	–1.90	0.07	***	0.15
45–54 years	–0.34	0.07	***	0.71
55–64 years	0.17	0.06	**	1.18
65–74 years	0.14	0.07	*	1.15
75–84 years	0.05	0.07		1.06
85 years and older (reference)	0	–		1
NUTS-2 region				
Burgenland	0.25	0.05	***	1.29
Carinthia	0.10	0.05	*	1.10
Lower Austria	–0.03	0.03		0.97
Upper Austria	–0.04	0.03		0.96
Salzburg	–0.07	0.05		0.93
Styria	–0.07	0.04	*	0.93
Tyrol	0.14	0.04	***	1.15
Vorarlberg	0.06	0.05		1.07
Vienna (reference)	0	–		1
Calendar year (time trend)	–0.02	0.00	***	0.98
Indicator: Styria since 2006	0.26	0.06	***	1.29
Indicator: Carinthia 1995–1998	–0.05	0.08		0.95

Note: * p<0.05, ** p<0.01, *** p<0.001. The intercept parameter depends on the coding of the other parameters, so its p-value has no meaning. The quasi-likelihood dispersion parameter for this model was estimated 1.10.

3.1.1 Example: Incidence of head and neck cancer for males

Table 3 contains the estimated regression parameters and their estimated standard errors of model (1) for male incidence of head and neck cancer (ICD-10 C00–C10 and C31–C32) of the base period from 1994 to 2009. Logged population size (person-years lived) was included as an offset parameter, i.e., its regression coefficient was fixed at 1. The estimated trend parameter is –0.0152, meaning that holding other factors constant, male head and neck cancer incidence is estimated to decline by around 1.5% annually. The parameters in the table refer to the logged cancer incidence count. If the estimated parameter is close to zero, then the linear change in the logged count approximates the proportional change in the proper count. The standard error indicates that this trend is significantly different from zero ($p < 0.001$), i.e., conditional on all other covariates, male head and neck cancer incidence risk did actually decline in the 1994–2009 period.

Incidence risk increases with age from the youngest age group (here pooled 0–34 years) to a maximum at 55–64 years. For higher ages, estimated parameters are again

smaller, although without statistically significant difference from the maximum. To account for the observed regional variation in incidence risk, we included two special regressors in this model. The fixed effect for Styria from calendar year 2006 onward indicates a 29% increase of completeness of case ascertainment due to an additional pathology database, and an effect for Carinthia in 1995–1998 indicates a 5% underestimation in the initial years of the regional cancer registry. The dispersion parameter is estimated at 1.10, indicating some unobserved heterogeneity in our data.

3.1.2 Estimated trend parameters

Tables 4 and 5 show the estimated trend parameters for all 56 models, multiplied by 100. We present estimated trend parameters and standard errors for the models where a common time-trend parameter was applied to all nine NUTS-2 regions (like the exemplary model in Table 3). We further present the range of estimated parameters (i.e., minimum to maximum) for the models where different trend parameters were estimated for different (groups of) NUTS-2 regions.

Table 4: Estimated time-trend parameters (×100) for cancer incidence models

Tumor site	ICD-10 code	Time-trend parameter (×100) for incidence models			
		Male incidence		Female incidence	
		Estimated trend parameter	Estimated standard error	Estimated trend parameter	Estimated standard error
Head and neck	C00–C10, C31–C32	–1.52	0.22	0.50	0.36
Stomach	C16	–4.58	0.09	–4.50	0.09
Colon, rectum, and anus	C18–C21	–2.18 – –0.17	–	–2.52	–0.20
Pancreas	C25	0.24	0.11	0.58	0.11
Trachea, bronchus, and lung	C33–C34	–1.49	0.06	2.25	0.09
Melanoma of skin	C43	–1.33 – 4.79	–	–2.19 – 1.25	–
Breast	C50	0.80	–0.40	–0.54	0.14
Cervix uteri	C53	–	–	–5.38 – –4.06	–
Corpus and uterus, not other specified	C54–C55	–	–	–3.10 – –1.02	–
Ovary	C56	–	–	–3.14	0.24
Prostate	C61	–3.18	0.27	–	–
Kidney	C64	–1.07	0.17	–2.26	0.23
Bladder	C67	–7.37 – –2.89	–	–2.41	0.43
Brain and nervous system	C70–C72	1.08 – 2.52	–	0.13	–0.50
Lymphoid, hematopoietic, and related tissue	C81–C96	–0.68 – 2.20	–	–1.00 – 2.81	–
Other and unspecified	Other C, excl. C44	0.29	0.06	–1.24 – –0.46	–

Note: Original parameters and standard errors multiplied by 100. If more than one time-trend parameter was estimated, the range (minimum to maximum) of estimated parameters is given.

In accordance with decreasing all-site age-standardized rates, estimated trend parameters were negative for most tumor sites. Stomach cancer incidence and mortality rates for both males and females are forecast to decrease by 4% to 5% annually, controlling for age, region, and specific dummy variables. Male prostate cancer incidence and mortality risks are forecast to decline by around 3% annually. For most tumor sites, incidence and mortality trend parameters point in a similar direction, although they may be of different magnitude. Regarding colon cancer for example, the incidence rate is forecast to decline by around 2%, but the mortality rate by around 4% per year, implying that the mortality/incidence ratio is predicted to decline. For female breast cancer, we forecast an annual decline in incidence risk by 0.5% and in mortality risk by 1.4%.

A single trend parameter for all regions was estimated in 42 models and regionally different trends in 14 models. Regional variation in trends was found more often for incidence than for mortality and was most pronounced in melanoma, brain, and nervous system cancers and cancers of lymphoid, hematopoietic, and related tissues.

For most tumor sites, estimated trend parameters were comparable between males and females. However, for lung cancer, we forecast a strong decrease in the future incidence and mortality rate for males, but a further increase for females. A comparable disparity between men and women is forecast for head and neck cancers. We also estimated different parameter signs between males and females for the residual category 'other and unspecified' tumor site.

3.2 Predicted future cancer counts and age-standardized rates

3.2.1 Aggregate (all-site) outcomes

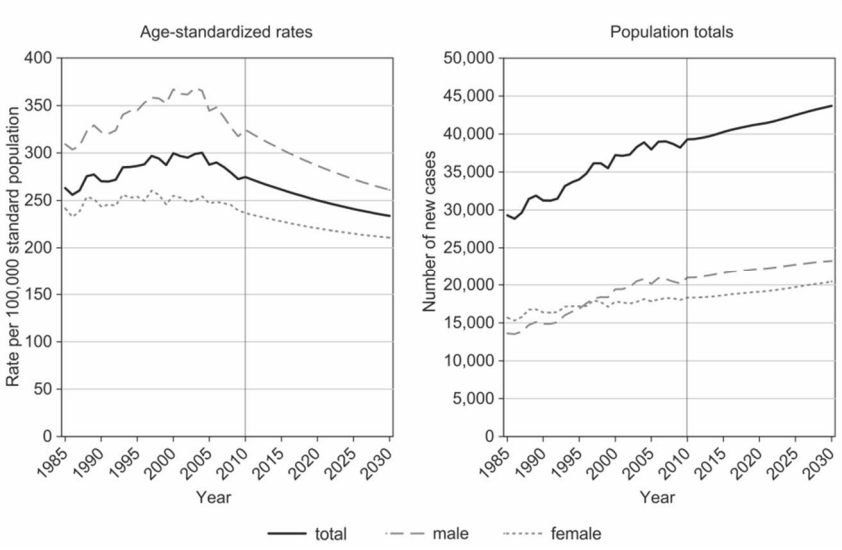
Figure 2 shows observed (1985–2009) and predicted (2010–2030) age-standardized rates and counts of cancer incidence (ICD-10 C00–C96, excl. C44) in Austria. Overall, the absolute number of newly diagnosed cancer cases increased during the last decades in Austria. This trend is predicted to continue in the future, as newly diagnosed cancer cases will increase from 38,200 in 2009 to 41,300 in 2020 (+8%) and to 43,700 in 2030 (+14%). On the contrary, age-standardized incidence rates are predicted to decrease from 272 newly diagnosed cancers per 100,000 standard population in 2009 to 250 cases in 2020 and further to 234 cases in 2030. Despite rising population totals, the individual risk of being newly diagnosed with cancer will thus decline in the coming years, reflecting the mostly negative time-trend parameters given in Table 4.

Table 5: Estimated time-trend parameters (×100) for cancer mortality models

Tumor site	ICD-10 code	Time-trend parameter (×100) for mortality models			
		Male mortality		Female mortality	
		Estimated trend parameter	Estimated standard error	Estimated trend parameter	Estimated standard error
Head and neck	C00–C10, C31–C32	–1.43	0.27	2.36	0.46
Stomach	C16	–4.87	0.14	–4.34	0.15
Colon, rectum, and anus	C18–C21	–3.47	0.52	–4.47	0.64
Pancreas	C25	–1.51	0.55	0.38	0.53
Trachea, bronchus, and lung	C33–C34	–1.71	0.10	1.77	0.16
Melanoma of skin	C43	–1.53 – 1.16	–	1.40	0.38
Breast	C50	–0.85	1.03	–1.35	0.48
Cervix uteri	C53	–	–	–4.84 – –1.67	–
Corpus and uterus, not other specified	C54–C55	–	–	–2.69	0.22
Ovary	C56	–	–	–2.54	0.67
Prostate	C61	–2.85	0.72	–	–
Kidney	C64	–3.24	0.57	–2.85	0.83
Bladder	C67	–1.80	0.22	–1.73	0.54
Brain and nervous system	C70–C72	–0.28 – 2.07	–	–0.03 – 2.26	–
Lymphoid, hematopoietic, and related tissue	C81–C96	0.29	0.17	0.76	0.16
Other and unspecified	Other C, excl. C44	0.57	0.31	–0.86	0.32

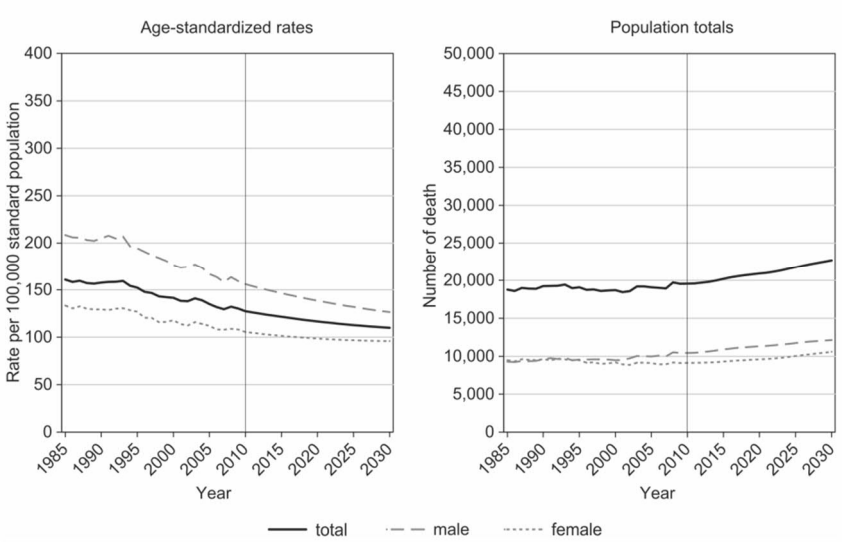
Note: Original parameters and standard errors multiplied by 100. If more than one time-trend parameter was estimated, the range (minimum to maximum) of estimated parameters is given.

Figure 2: Observed (1985–2009) and predicted (2010–2030) incidence, all cancers



Observed and predicted age-standardized rates and counts of cancer mortality are shown in Figure 3. Predicted evolutions are similar to cancer incidence: The absolute number of cancer deaths will increase from 19,500 in 2009 to 20,900 in 2020 (+7%) and to 22,700 in 2030 (+16%). In contrast, age-standardized cancer mortality rates will decrease from 130 deaths per 100,000 standard population in 2009 to 117 in 2020 and then to 110 in 2030.

Figure 3: Observed (1985–2009) and predicted (2010–2030) mortality, all cancers



The predicted increase in the absolute cancer incidence and cancer death counts is thus solely caused by population aging. In the prediction period until 2030, those age groups most prone to develop and die from cancer will largely increase. If population size and age structure remained constant in the future, then the absolute numbers of cancer incidence and cancer deaths would actually decline, as age-standardized rates confirm. This can be further illustrated by comparing our model predictions (3) with the outcomes obtained by the alternative constant rates scenario (Table 6). In the alternative scenario, the total cancer incidence count increases to 49,400 newly diagnosed cancers in 2030. The relative difference between our model prediction and the alternative constant rates scenario is even greater for mortality, where the latter would predict 26,900 cancer deaths in 2030. An interpretation of the slower increase in our model prediction is that medical and social progress (such as new treatments, better early

detection of cancers, or the reduction in tobacco smoking) dampens the aging-induced increase in cancer incidence and mortality.

Table 6: Comparison of model prediction with alternative constant rates scenario

Prediction outcome	Population totals			Predicted percentage change	
	Observed in 2009	Predicted for 2030			
		Model (3)	Constant rates scenario	Model (3)	Constant rates scenario
Incidence (newly diagnosed cancers)	38,218	43,706	49,449	+14.4	+29.4
Mortality (cancer deaths)	19,547	22,707	26,909	+16.2	+37.7

3.2.2 Site-specific outcomes

Table 7 presents the Austrian totals of newly diagnosed cancer cases and cancer deaths observed in 2009 and predicted for 2030, disaggregated by sex and tumor site. Values for 1983–2008 (observed) and for 2010–2029 (predicted) are available on request from the authors. Colon cancer incidence is predicted to increase among males but decrease among females. Colon cancer mortality is predicted to decline substantially among both sexes. Lung cancer diagnoses and deaths will remain rather constant among males but double among females. In 2030, more women than men will be newly diagnosed with lung cancer. Female breast cancer incidence will increase by about 10%, but deaths will decline by about 10% in 2009–2030. Some decline is also predicted for prostate cancer deaths. Stomach cancer incidence and mortality will decrease in the coming years. In contrast, newly diagnosed cases and deaths will rise for melanoma of skin, brain, and nervous system cancers, and cancers of lymphoid, hematopoietic, and related tissues.

Table 7: Predicted population totals of cancer incidence and cancer deaths by sex and tumor site

Tumor site	ICD-10-code	Cancer incidence: newly diagnosed cases				Cancer mortality: cancer deaths			
		Males		Females		Males		Females	
		Observed in 2009	Predicted for 2030	Observed in 2009	Predicted for 2030	Observed in 2009	Predicted for 2030	Observed in 2009	Predicted for 2030
All cancers	C00–C97, excl. C44	20,197	23,272	18,021	20,434	10,426	12,124	9,121	10,583
Head and neck	C00–C10, C31–C32	864	820	282	409	355	370	128	269
Stomach	C16	775	455	601	322	517	286	406	240
Colon, rectum, and anus	C18–C21	2,730	3,051	2,037	1,689	1,175	875	969	528
Pancreas	C25	717	1,148	769	1,199	703	721	721	1,078

Table 7: (Continued)

Tumor site	ICD-10-code	Cancer incidence: newly diagnosed cases				Cancer mortality: cancer deaths			
		Males		Females		Males		Females	
		Observed in 2009	Predicted for 2030	Observed in 2009	Predicted for 2030	Observed in 2009	Predicted for 2030	Observed in 2009	Predicted for 2030
Trachea, bronchus, and lung	C33–C34	2,829	2,958	1,531	3,208	2,386	2,380	1,174	2,256
Melanoma of skin	C43	668	1,596	659	955	188	307	125	236
Breast	C50	49	99	5,103	5,636	12	20	1,594	1,463
Cervix uteri	C53	–	–	412	175	–	–	141	82
Corpus and uterus, not other specified	C54–C55	–	–	936	962	–	–	276	203
Ovary	C56	–	–	729	464	–	–	489	386
Prostate	C61	4,945	3,902	–	–	1,125	1,043	–	–
Kidney	C64	716	895	500	412	263	173	185	131
Bladder	C67	1,218	1,011	428	358	300	372	164	154
Brain and nervous system	C70–C72	353	650	329	416	279	521	226	438
Lymphoid, hematopoietic, and related tissue	C81–C96	1,463	2,344	1,290	1,684	846	1,361	830	1,297
Other and unspecified	Other C, excl. C44	2,870	4,346	2,415	2,545	2,277	3,693	1,693	1,821

Note: Predicted values are in general not integer-valued. In this table, predictions were rounded conventionally to next integers.

4. Discussion

4.1 Summary and comparison with international findings

The current paper aimed at predicting future cancer incidence and mortality rates for Austria in the midterm perspective up to 2030. Technically speaking, our prediction was a secondary population projection, i.e., we used a given population projection and applied forecasted cancer incidence and mortality rates to it. To our knowledge, ours is the first prediction of cancer cases that combines population projections with future rates obtained by quasi-likelihood regression models.

The key finding of our prediction was that absolute numbers of cancer incidence and mortality will rise in the future, whereas the individual risk will decline. This apparently paradoxical finding is caused by demographic aging. Most cancers are diseases of the elderly, and their number will rise substantially in the coming decades as a long-run consequence of high fertility in the late 1950s and early 1960s. The effect of this shift in age structure can be illustrated by comparing the outcomes of our prediction with the alternative constant rates scenario, which would result in an increase in 2009–2030 in cancer incidence totals by 29% (compared to 14% in our prediction) and in cancer death totals by 38% (compared to 16% in our prediction). A rise in absolute numbers accompanied by a decline in age-standardized rates has also been found by

other authors (French, Catney, and Gavin 2006; Mistry et al. 2011; Rapiti et al. 2014). In the United States, the total cancer incidence is projected to increase by approximately 45% by 2030 (Smith et al. 2009).

We found decreasing trend parameters in the male and female cancer burden for most tumor sites. For lung cancer, however, we forecast a strong decrease in future incidence and mortality risk for males but a further increase for females. This difference is most likely a consequence of gender-specific behavioral changes because females are currently more likely to smoke, and males are less likely to do so compared to past decades (Statistik Austria 2015). To address this strong trend, also observable in other industrialized countries, Dyba and Hakulinen (2008) even sometimes exclude respiratory cancers from their cancer predictions. Respective predictions are also comparable for other countries. In Switzerland, age-standardized female lung cancer will increase by +48% by 2019, compared to +13% for males (Rapiti et al. 2014). On the contrary, little sex-specific variation in lung cancer trends up to 2030 is predicted for the United Kingdom (Mistry et al. 2011) and the United States (Smith et al. 2009). In a dynamic population health model using data from nine European countries, Lhachimi et al. (2016) estimated that smoking leads to 0.7 years and about 600,000 lives lost for males and 0.9 years and 700,000 lives lost for females. Although overall cancer incidence and death rates will decrease in Austria, the alarming lung cancer trends among women emphasize the need for evidence-based tobacco control interventions (Jemal et al. 2008).

Likewise, future head and neck cancer rates will increase in women but decrease in men. This finding is in line with a pooled analysis of international data conducted by Hashibe et al. (2009). As this tumor entity is also associated with smoking habits, this observation mirrors the trend seen in lung cancer. In addition to smoking and chewing tobacco products, alcohol use has been linked to head and neck cancer risk (Curado and Hashibe 2009; Roswall and Weiderpass 2015). One might speculate that with the social acceptance of tobacco and alcohol habits, women are adopting lifestyle habits that increase health risk previously accredited as "male" behavior (Wilsnack et al. 2018). Increasing both tobacco and alcohol prices could be feasible population-based measures to tackle unhealthy lifestyle habits (Turiano et al. 2015; Lhachimi et al. 2016).

We also estimated different parameter signs between males and females for the residual category "other and unspecified tumor site (other C, excl. C44)." However, this category is difficult to interpret due to its per se indistinctive nature. Thus, predictions concerning malignancies that fall into this category might benefit from specific research questions and assessments on a site-by-site basis, taking into account the site-specific trends and clinical features.

Regional variation in trends was most pronounced in cancers of lymphoid, hematopoietic, and related tissues as well as cutaneous melanoma. Regarding the latter

and given that Austria is a predominantly mountainous country, an ecological study found that melanoma incidence rates increased, whereas mortality rates decreased with altitude of place of living (Haluza, Simic, and Moshammer 2014). The observed diverging incidence and mortality trends might be explained by diagnosis at earlier tumor stages due to better screening adoption in these regions and vitamin D-driven slower tumor progression (Monshi et al. 2016). Also, upwelling radiation caused by, e.g., sunlight reflected by snow cover, could also explain higher melanoma incidence rates with altitude (Schrempf et al. 2016).

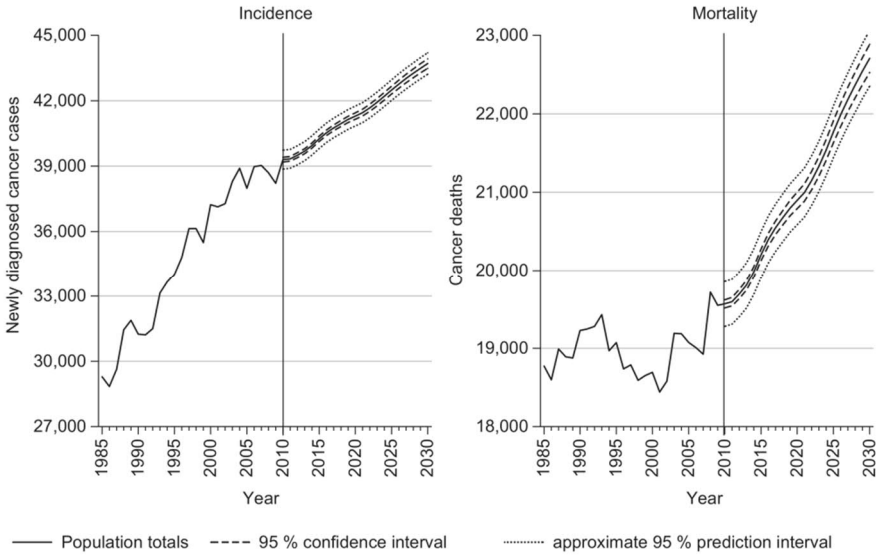
4.2 Uncertainty in our model predictions

Any prediction of future events naturally comes with uncertainty. As a general rule, the degree of uncertainty depends on the time horizon (the closer to the present, the more accurate) and on the plausibility and robustness of the underlying assumptions. Since our method combines two sources, a primary population projection and statistical model estimates, the overall uncertainty of our prediction has two components. In the following, we take the primary population projection as given and focus on uncertainty in the statistical model estimates.

4.2.1 Reliability

Figure 4 shows the ranges of random error of our model predictions for all tumor sites combined. Confidence intervals of 95% for the conditional expectations and approximately 95% prediction intervals for single observations were calculated for each statistical model according to Cameron and Trivedi (1998: 84). Model-specific variances were then added over tumor sites and sexes, assuming statistical independence. Vertical axes were cut off to make intervals more visible in Figure 4.

Figure 4: Prediction intervals for cancer incidence and cancer death counts



For the overall cancer incidence count in 2030, which we predict as 43,700, the confidence interval for the conditional expectation ranges from 43,500 to 43,900, and an approximate prediction interval for the actual outcome ranges from 43,200 to 44,200. For cancer death counts in 2030, predicted as 22,700, the confidence interval ranges from 22,500 to 22,900, and the approximate prediction interval from 22,300 to 23,100. So by any measure, uncertainty in our prediction caused by chance variation in the base period data is low and predictions are statistically reliable.

4.2.2 Validity

Validity of our forecasts stands and falls with the correct specification of the conditional expectation in the forecast period, i.e., that (1) actually holds until 2030. In contrast to chance variation, systematic error cannot be quantified, although some insights are revealed. In the base period 1983–2009 corresponding to 27 calendar years, we identified structural breaks in time trends in 28 instances, i.e., in just half of all models. Therefore, starting years are later than 1983 in Table 1. So a forecast horizon of

21 years is rather the upper limit of plausibility of assuming stable structural relationships.

Our model is essentially an exponential extrapolation of past trends into the future. We explicitly accounted for age structure and regional disparities and for known data artifacts such as changes in completeness of incidence case registration due to introduction of regional cancer registries during the base period. Developments such as change in risk behavior or medical and social progress are implicitly accounted for by the trend parameter. At least for prediction of all cancers combined, such superficially simple methods have often been found to be more useful than more sophisticated models that account for complex factors such as behavioral changes or population trends (Dyba and Hakulinen 2008; Statistik Austria 2015).

For some tumor sites in particular, estimated age group effects might be confounded by birth cohort effects, so age-specific forecasts might be somewhat biased. We abstained from accounting for birth cohorts in the statistical models because the data does not directly enable birth cohorts to be identified, and determining which cohort effects could be relevant for so many different models is not straightforward. Nevertheless, for forecasting specific cancer sites, e.g., female lung cancer, models that include cohort effects might be superior to our general approach.

The exponential term in the conditional mean specification is useful for predicting declining rates because forecasted rates never reach or fall below zero; however, the exponential term is less useful for rising rates because forecasted rates expand over time. However, since our prediction horizon is somewhat short (until 2030) and most time-trend parameters are indeed negative, this difference does not greatly affect the overall results. In contrast, French et al. (2006) apply an alternative method where falling rates are extrapolated exponentially, but rising rates linearly.

Forecasting separate trends by tumor site and sex has the advantage that different age profiles, etiologies, and trends are accounted for. This flexibility comes with the risk of inconsistencies between forecasted rates. This risk is exemplified by a male-female crossover of predicted pancreas cancer mortality rates and a singular decline in incident melanoma of the skin in Vienna compared to increases in all other Austrian regions. The convergence of male and female lung cancer rates, on the other hand, is not necessarily an inconsistency but is probably a consequence of the long-run convergence of smoking rates between men and women (Hackl and Waldhoer 2013).

It is unclear from the outset whether incidence or mortality rates can be predicted more accurately. On the one hand, the data can be assumed to be more complete for mortality. On the other hand, cause-specific mortality projections are also subject to specific sources of uncertainty, such as changes in cause-of-death diagnosing and coding behavior. This difference is especially true for detailed outcomes such as projections for specific tumor sites.

5. Conclusion

In Austria, the absolute number of cancer cases increased continuously during the last decades. Our novel method combining population projections with quasi-likelihood models revealed that this trend will also continue in the near future due to the aging of the population, as cancer is primarily a disease of the elderly. On the contrary, age-standardized cancer incidence and mortality rates will decline substantially until 2030. Different trends are predicted by tumor site and for some tumor sites also by sex, region, or incidence vs. mortality.

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Appendix

Table A-1: Pooling of younger age groups in regression models, on the basis of incidences rates 2008–2010

Tumor site	ICD-10 code	Age-specific incidence rate in 2008–2010[#]						Pooled age group
		0–4	5–14	15–24	25–34	35–44	45–54	
Head and neck	C00–C10, C31–C32	0.3	0.0	0.4	0.8	4.0	19.7	0–34
Stomach	C16	0.0	0.0	0.0	1.1	2.9	8.7	0–34
Colon, rectum, and anus	C18–C21	0.0	0.1	0.7	2.3	9.2	30.8	0–24
Pancreas	C25	0.0	0.0	0.1	0.3	2.0	9.8	0–34
Trachea, bronchus, and lung	C33–C34	0.0	0.0	0.3	1.0	6.4	39.1	0–34
Melanoma of skin	C43	0.1	0.3	3.6	8.5	13.6	16.8	0–14
Breast	C50	0.0	0.0	0.6	7.4	36.9	80.5	0–24
Cervix uteri	C53	0.0	0.0	0.3	3.4	6.0	6.6	0–24
Corpus and uterus, not other specified	C54–C55	0.0	0.0	0.0	0.5	2.0	8.8	0–34
Ovary	C56	0.0	0.4	0.5	0.9	3.2	8.5	0–34
Prostate	C61	0.0	0.0	0.0	0.1	1.9	27.7	0–34
Kidney	C64	1.9	0.1	0.1	1.0	4.4	12.6	5–34
Bladder	C67	0.0	0.0	0.3	0.6	2.4	8.9	0–34
Brain and nervous system	C70–C72	3.5	2.5	2.0	3.3	4.3	8.1	–
Lymphoid, hematopoietic, and related tissue	C81–C96	6.1	4.6	7.6	7.8	11.4	22.9	–
Other and unspecified	Other C, excl. C44	4.1	3.0	10.0	21.8	30.7	58.3	–

Note: [#] Age-specific incidence rates are newly diagnosed cancers per 100,000 person-years lived in the same age group.

Table A-2: Regression models where regionally different trend parameters were applied

Tumor site	ICD-10 code	Outcome	(Groups of) NUTS-2 regions for which separate trend parameters were estimated[#]
Colon, rectum, and anus	C18–C21	Male incidence	Styria, Tyrol, Vorarlberg – All other
Melanoma of skin	C43	Male incidence	Burgenland, Lower Austria – Vorarlberg. Vienna – All other
		Female incidence	Tyrol, Vienna – All other
		Male mortality	Vienna – All other
Cervix uteri	C53	Female incidence	Carinthia, Upper Austria – All other
		Female mortality	Burgenland, Vienna – Salzburg – All other
Corpus and uterus not, other specified	C54–C55	Female incidence	Lower Austria – All other
Bladder	C67	Male incidence	Salzburg – All other
Brain and nervous system	C70–C72	Male incidence	Styria – All other
		Male mortality	Vienna – All other
		Female mortality	Vienna – All other
Lymphoid, hematopoietic, and related tissue	C81–C96	Male incidence	Salzburg, Tyrol, Vorarlberg – All other
		Female incidence	Salzburg, Vorarlberg – All other
Other and unspecified	Other C, excl. C44	Female incidence	Carinthia, Upper Austria, Tyrol – All other

Note: [#] Groups of NUTS-2 regions with separate trends parameters are separated by dashes. NUTS-2 regions within a group are separated by commas.

Table A-3: Estimated dispersion parameters

Tumor site	ICD-10 code	Quasi-likelihood dispersion parameter			
		Incidence		Mortality	
		Males	Females	Males	Females
Head and neck	C00–C10, C31–C32	1.10	1.00	1.04	1.02
Stomach	C16	1.05	1.03	1.03	1.05
Colon, rectum, and anus	C18–C21	1.13	1.07	1.09	1.02
Pancreas	C25	1.01	1.02	1.02	1.06
Trachea, bronchus, and lung	C33–C34	1.19	1.12	1.17	1.08
Melanoma of skin	C43	1.16	1.21	0.98	1.01
Breast	C50	0.96	1.21	0.93	1.02
Cervix uteri	C53	–	1.14	–	1.06
Corpus and uterus not, other specified	C54–C55	–	1.05	–	1.07
Ovary	C56	–	1.05	–	1.06
Prostate	C61	1.50	–	1.03	–
Kidney	C64	1.04	1.01	1.00	1.06
Bladder	C67	1.13	1.04	1.02	1.01
Brain and nervous system	C70–C72	1.01	1.02	1.02	1.03
Lymphoid, hematopoietic, and related tissue	C81–C96	1.03	1.03	1.03	1.02
Other and unspecified	Other C, excl. C44	1.14	1.31	1.09	1.07